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24 is found in claim 9 as filed. Support for claim 25 is found in claim 10 as filed. Support for claim 26 is found at p. 11 as filed. Support for claims 27 and 41 is found at p. 31, line 33 to p. 32, line 14 and in claim 13 as filed. Support for claim 29 is found at p. 45, lines 19-20 and claim 3 as filed. Support for claim 30 is found at p. 46, line 19. Support for claims 31 and 36 is found throughout the specification and in claims 4, 5, 7 and 16 as filed. Support for claim 38 is found in claim 4 as filed.

Response to Rejection Under 35 U.S.C. § 112

The Examiner has rejected claims 1-16 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Applicants thank the Examiner for his helpful suggestions. The rejection is now moot in view of the newly drafted claims 17-41. Applicants submit that the claims are now in condition for allowance and request early notification of such.

Response to Rejection Under 35 U.S.C. § 103

The Examiner has rejected Claims 1-12 and 15-16 under 35 U.S.C. § 103 as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524, "Nikiforov") in view of Walt et al. (U.S. Patent No. 6,023,540, "Walt"). As a preliminary matter, the original claims have been cancelled and new claims 17-41 have been added.

Nikiforov teaches a ligase and polymerase-mediated method for determining the identity of a nucleotide at a preselected site in a nucleic acid molecule. The method

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provides a hybridization complex comprising a target sequence, a first oligonucleotide, and a second oligonucleotide. The first and second oligonucleotides are separated by the preselected site. The complex is incubated with a polymerase, a ligase and nucleoside triphosphate mixture under conditions to allow the incorporation of the NTP and ligation of the (now) adjacent first and second hybridized oligonucleotides. The nucleotide at a detection position is determined. The first oligonucleotide is covalently attached to a solid support, such as a bead.

Nikiforov does not teach the microsphere positioned on a surface. Nikiforov also does not teach the method comprising a plurality of detection probes (Claims 4 and 5, analogous to new claim 38), does not teach each NTP comprises a unique fluorophore (Claim 8, analogous to new claim 23), and does not teach the label of Claims 10 and 11 (analogous to new claims 25 and 26) comprise imine-biotin or a functional group for addition of a fluorophore.

Walt teaches microspheres on a surface, and also teaches a method for providing a hybridization complex comprising a target sequence and a capture probe covalently attached to microspheres on a surface of a substrate.

The present invention is directed to a variety of methods for determining the identification of a nucleotide at a detection position in a target sequence, wherein said methods utilize microspheres on a surface of a substrate and comprise single base extension methods, oligonucleotide ligation amplification methods, invasive cleavage methods, competitive hybridization methods and novel combinations of these methods.

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As the Examiner is aware, a *prima facie* case of obviousness requires that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." (MPEP § 2143).

The requirement that there be some suggestion or motivation to modify or combine references to obtain the claimed invention has not been satisfied in this instance.

With particular reference to new claims 21-26, 27-31, 38, 39, and 41, Nikiforov does not teach or suggest single base extension (claims 21-26 and 39), the use of structure specific enzymes (claims 27-31 and 41), or competitive hybridization on beads (claim 38). The Examiner contends that the motivation to position microspheres on a surface would be supplied through the "expected benefit of individually detecting thousands [of] detection positions." The Examiner provides no support for this contention.

Furthermore, the Examiner contends that the motivation to modify the nucleotide detection of Nikiforov to comprise a plurality of probes would be supplied by prior art knowledge of "the obvious benefit of detecting any and all possible nucleotides at the detection position of the target sequence." Again, the Examiner provides no support.

With regard to Claim 8 (analogous to new claim 23), the Examiner contends that the motivation to modify the fluorescently detectable NTPs of Nikiforov with each NTP comprising a unique fluorophore would be supplied by prior art knowledge of the

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"obvious benefit of determining the NTP by detecting the unique fluorophore and the known benefit of combining all 4 NTPs in one assay and thereby economizing time, labor and costs." This statement is not supported.

Finally, with regard to Claims 9-11 (analogous to new claims 24-26), the Examiner contends that the motivation to modify the haptens of Nikiforov with routinely practiced haptens would be "based on available reagents and equipment and for the benefit of convenience and economy." Again, there is no support for the statement.

The Applicants respectfully draw the Examiner's attention to M.P.E.P. §2144.03, which states that while an Examiner can take official notice of facts outside the record, these must be "capable of instant and unquestionable demonstration as being 'well-known' in the art"; the section goes on to state that if the Applicants traverse such an assertion the Examiner should cite a reference in support of the position.

Likewise, neither Walt nor the prior art teach that Nikiforov's method can be or should be improved by utilizing a plurality of probes, by having each NTP comprise a unique fluorophore, or by utilizing labels comprising imine-biotin or a functional group for addition of a fluorophore.

The Applicants, therefore, traverse and respectfully submit that none of the Examiner's statements regarding the expected benefits of the above mentioned improvements are sufficient motivation under the law.

Furthermore, Applicants submit that the Examiner has failed to point to the teachings in either of the references that would have motivated the skilled artisan to

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combine the teachings of Nikiforov and Walt. While the Examiner has noted components of each reference, Applicants submit that the prior art makes no suggestion to modify these components to reach the present invention. Rather, the Examiner appears to be using obviousness to provide the motivation to modify the references, which is legally incorrect. The mere fact that a reference can be modified does not render the resultant modification obvious unless the prior art also provides the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Accordingly, a *prima facie* case of obviousness has not been met and the rejection should be withdrawn.

The Examiner has rejected Claims 13 and 14 under 35 U.S.C. § 103 as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524, "Nikiforov") in view of Walt et al. (U.S. Patent No. 6,023,540, "Walt"), as applied to Claims 1 and further in view of Lyamichev et al. (Nature Biotechnology, 17:292 (1999), "Lyamichev").

Nikiforov and Walt are discussed above.

Lyamichev teaches identification of polymorphisms by invasive cleavage methods.

With regard to claim 13 (analogous to new claim 27), the Examiner contends it would have been *prima facie* obvious to one of skill in the art to modify the method of Nikiforov with the teachings of Walt and Lyamichev to obtain the claimed invention

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because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the nucleotide detection of Nikiforov with the hybridization and cleavage of Lyamichev for the expected benefits of quantitative detection of a single nucleotide without amplification and the elimination of the primer extension reactions as taught by Lyamichev. The Examiner further contends that the skilled practitioner would have been motivated to modify the microspheres of Nikiforov with the microspheres on the surface of a substrate for the expected benefit of individually detecting thousands [of] detection positions. Applicants traverse.

As argued above, Applicants submit that the Examiner has failed to point to the teachings in any of the references that would have motivated the skilled artisan to combine the teachings of Nikiforov, Walt, and Lyamichev. While the Examiner has noted components of each reference, Applicants submit that the prior art makes no suggestion to modify these components to reach the present invention. Rather, the Examiner appears to be using obviousness to provide the motivation to modify the references, which is legally incorrect. The mere fact that a reference can be modified does not render the resultant modification obvious unless the prior art also suggests the desirability of the combination; see *In re Mills*, supra.

Again, a *prima facie* case of obviousness requires that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." (MPEP § 2143).

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Applicants submit there is no suggestion or motivation in the references, taken alone or in combination, to combine the reference teachings.

The motivation to combine references due to "an obvious benefit of eliminating probe and/or target labeling steps" or "for the ease of supporting thousands of separate chemical functionalities" is legally incorrect under M.P.E.P. §§ 2143 and 2144.03, without the references themselves providing the desirability of the combination.

CONCLUSION

None of the cited references taken alone or in combination renders the claimed invention obvious to one of skill in the art at the time the invention was made. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection should be withdrawn.

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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